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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,777	04/09/2004	Glauco P. Tocchini-Valentini	911076.90023	1445
26710	7590	07/05/2007		
QUARLES & BRADY LLP 411 E. WISCONSIN AVENUE SUITE 2040 MILWAUKEE, WI 53202-4497			EXAMINER SHIN, DANA H	
			ART UNIT 1635	PAPER NUMBER
			MAIL DATE 07/05/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/821,777	TOCCHINI-VALENTINI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 18-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1-27-2005</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election of claims 1-17 in the reply filed on March 8, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### ***Status of Claims***

Claims 1-23 are pending. Claims 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 1-17 are currently under examination on the merits.

### ***Specification***

The disclosure is objected to because of the following informalities:

1) Paragraph 0002 is left blank. It is unclear whether or not a piece of disclosure is missing. Clarification is required.

2) It appears that the word "tNRA" in paragraph 0006 is a typographical error. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-17 depend from claim 1, which claims a method of cleaving a target RNA molecule wherein the target molecule is in the bulge-helix-bulge conformation, and wherein the target molecule does not comprise a tRNA structure.

It is unclear and ambiguous how the target RNA molecule can comprise the BHB conformation but does not comprise a tRNA structure. The BHB conformation is a hallmark of a tRNA structure, and therefore, one of ordinary skill in the art cannot determine the structure of the target RNA molecule claimed in the instant case, because the claim language is treating as if the BHB conformation and the tRNA structure are mutually exclusive, when in fact, they are not. Therefore, it is deemed that the structure of the target RNA molecule is indeterminate, thereby rendering the claims indefinite. For claim interpretation, the target RNA molecule will be construed as not having the tRNA structure in its native or natural form, but artificially induced to form the BHB conformation.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

Note that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the specification provides a single species, mouse profilin 1 mRNA, which is complexed with another oligoribonucleotide thereby allowing formation of a BHB and therefore is cleaved by a tRNA endonuclease. See paragraph 0086. The method of cleaving mouse profilin 1 mRNA exemplified in the specification is not a representative number of species embraced by the genus of a "method of cleaving a target RNA molecule", wherein the target RNA is neither a natural tRNA nor has the BHB conformation in its native state. The

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disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure “indicates that the patentee has invented species sufficient to constitute the gen[us].” See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004), which stated “[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.” See also MPEP §2163.

In light of the above, the instant specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented the genus embraced by the method of cleaving a target RNA molecule that does not inherently comprise a tRNA structure.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fabbri et al. (*Science*, 1998, 280:284-286, applicant's citation filed 1-27-2005) in view of Santoro et al. (*PNAS*, 1997, 94:4262-4266).

The claims are drawn to a method of cleaving a target RNA molecule comprising exposing the target molecule to an eukaryotic tRNA splicing endonuclease or a heterologous archaeal tRNA splicing endonuclease, wherein the target molecule is in the BHB conformation, wherein the cleavage occurs within the BHB and the target molecule does not comprise a tRNA structure, wherein BHB conformation is obtained by hybridizing the target molecule with an oligonucleotide designed to form a BHB conformation, wherein the target molecule is an mRNA, the cleavage occurs within a cell *in vitro* and *in vivo*, wherein the cell is mammalian and a eukaryotic cell.

Fabbri et al. teach that both archaeal and eukaryotic tRNA endonucleases recognize and cleave the RNA substrate at the UA sequence site within the BHB motif. See entire reference. Fabbri et al. do not teach a method of cleaving a target RNA molecule that does not naturally comprise a tRNA structure by exposing the RNA to an eukaryotic tRNA splicing endonuclease.

Santoro et al. teach that DNAzymes have invariant catalytic motifs as well as cleavage positions. See Figure 2. Based on the structural requirements of the DNAzymes for the substrate cleavage, Santoro et al. teach that they constructed a DNAzyme that cleaves HIV-1 RNA at an AU site by incorporating the 10-23 motif shown in Figure 2. See also pages 4265-4266. They

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teach that DNAzymes or ribozymes can be designed to target a sequence-specific substrate by incorporating art-recognized structural requirements (e.g., catalytic motifs and cleavage nucleotides) for the cleavage activity of the DNAzymes or ribozymes (pages 4265-4266). They teach that the 10-23 DNAzyme will be used as an agent that inhibits target gene expression by acting as a sequence-specific endoribonuclease. See last paragraph of the reference on page 4266.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the BHB motif-mediated cleavage activity of tRNA splicing endonucleases of Fabbri et al. to a method of cleaving a target RNA sequence by adopting the similar cleavage mechanism of DNAzymes as taught by Santoro et al.

One of ordinary skill in the art would have been motivated to utilize the sequence(UA)- and motif (BHB)-specific tRNA splicing endonuclease cleavage activity into a method of cleaving a target RNA molecule by artificially inducing the formation of the BHB conformation in the substrate (or target) RNA, because it would have been apparent to the skilled artisan that both DNAzyme and tRNA splicing endonuclease act as sequence-specific endoribonucleases and therefore would have seen that tRNA splicing endonucleases can be used as DNAzymes are utilized in the art, that is, as an agent that inhibits target gene expression. One of ordinary skill in the art would have seen the potential utility of tRNA splicing endonuclease as an enzyme that can be used to direct cleavage of a target RNA molecule by taking the BHB-motif requirement into consideration as taught by Fabbri et al., because it was known in the art to cleave a target RNA molecule by designing a DNAzyme by incorporating art-recognized structural requirements (e.g., catalytic motifs and cleavage nucleotides) as taught by Santoro et al. In other



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words, one of ordinary skill in the art would have been motivated to combine the teachings of the prior art with a reasonable expectation of success because site-specific and motif-specific cleavage of a target RNA was well-recognized technology to suppress target gene expression in cells as taught by Santoro et al., and because the essential and critical structural requirement for the efficient cleavage of target RNA by tRNA splicing endonuclease was known in the art as taught by Fabbri et al. Since one of ordinary skill in the art would have seen the similarities in the cleavage mechanism between the BHB motif-mediated cleavage at the UA sequence site of a tRNA splicing endonuclease and the AU sequence-mediated cleavage of a DNAzyme, it would have been obvious for the skilled artisan to devise a method of cleaving a target RNA molecule by inducing the formation of the BHB conformation in a target RNA molecule followed by contacting the RNA molecule with an eukaryotic tRNA splicing endonuclease. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

### ***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

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A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-17 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17 of copending Application No. 10/296,574. Claims 1-17 of the instant application are identical to claims 1-17 of 10/296,574 verbatim. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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